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## 13. ABSTRACT (Maximum 200 words)

The goal of the proposed studies is to characterize the effects of noradrenergic (NA) afferents on cortical information processing. Our previous studies indicate that the primate locus coeruleus (LC) system, originating in the pontine brainstem, innervates neocortex more densely than previously thought, exhibiting highly specific patterns in terms of the regional and laminar distribution of its axons. Our previous neurophysiological observations suggest that this system imposes state-related modulatory effects on thalamo-cortical and cortico-cortical systems.

The proposed studies have the following Specific Aims:  
1) To examine, in monkeys, the effects of manipulating the LC-NA system on ERPs, EEG characteristics, and associated

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behaviors in operant paradigms that utilize visual or auditory cues; 2) To correlate the activities of individual monkey LC-NA neurons with cortical neuronal activity and the measures utilized in Aim 1; 3) To extend our preliminary observation that activation of the LC by local drug infusion, in halothane-anesthetized rats, produces EEG signs of cortical and hippocampal activation; 4) To examine the relationship between the intensity of LC neuronal activity and rates of norepinephrine release in neocortex and hippocampus by performing microdialysis in these forebrain terminal regions in anesthetized rats during manipulation of LC activity.

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SECOND ANNUAL TECHNICAL REPORT  
(01 Jul 91-30 Jun 92)

CONTRACT: AFOSR-90-0325 (Foote/Pineda/Berry)

TITLE: Extrathalamic Modulation of Cortical Function

PRINCIPAL INVESTIGATORS: Stephen L. Foote/Jaime A. Pineda

DATE: 15 August, 1992

**Organization of Technical Report.** This report is divided into four sections that correspond to the Specific Aims for Years 04-06. Full-length reports published, accepted for publication, or submitted since the previous Technical Report are listed at the end of this report. The numbers in square brackets in the text refer to the corresponding publication from this list.

**AIM 1: TO EXAMINE, IN MONKEYS, THE EFFECTS OF MANIPULATING THE LC-NA SYSTEM ON EVENT-RELATED POTENTIALS (ERPs), ELECTROENCEPHALOGRAPHIC (EEG) CHARACTERISTICS, AND ASSOCIATED BEHAVIORS IN OPERANT PARADIGMS THAT UTILIZE VISUAL OR AUDITORY CUES.**

**The effects of systemically administered adrenergic agents on monkey P300s.** [Publications 2 and 3] These studies have evaluated the role of norepinephrine in the modulation of auditory and visual P300 responses. Waveforms were recorded in squirrel monkeys (*Saimiri sciureus*) using paradigms in which auditory and visual "oddball" stimuli occurred pseudorandomly in a repetitive background of auditory or visual events. P3-like potentials were recorded following the infrequent stimuli in the two paradigms (auditory- and visual-background). Visual P3s were larger in amplitude and longer in latency than auditory P3s. Scalp topographies also differed, with auditory P3s exhibiting distinct centro-parietal maxima while visual P3s exhibited a more fronto-central distribution. These differences suggest distinct neural generators, a finding consistent with new evidence for modality-specific influences on the human P300. The role of norepinephrine was examined by recording ERPs before and after the administration of L657,743, an alpha-2 antagonist. Drug administration resulted in reduced auditory and visual P3 potentials at parietal sites. Only auditory P3s were reduced at midline electrodes, while visual P3s were enhanced. No effects were noted at temporal sites. The data support the hypothesis that cortical norepinephrine is a modulatory mechanism common to auditory and visual P3s. However, other factors appear to influence the direction of modulation at midline and parietal sites. These data support the existence of at least two distinct cortical P3 sources, one located in midline-temporal and the other in parietal brain regions.

**Active and Passive Processing of Faces.** [Publication 5] These studies examined ERP responses to face stimuli during passive and active conditions in one juvenile and 2 young adult macaque (*Macaca fascicularis*) monkeys. Subjects viewed tachistoscopically-presented pairs of faces in four possible combinations: human-human, monkey-monkey, monkey-human, and human-monkey. In the first experiment, faces were presented upright. Then, one monkey was trained to

associate the occurrence of a monkey-monkey pair of faces with juice reward. In the subsequent experiment, the same stimuli were presented inverted. In all experiments, monkey ERPs exhibited a P1-N1-P2 complex of peaks in the 400 ms following stimulus presentation. However, only upright faces elicited a prominent, widely-distributed negativity (N4) in the 400-800 ms interval, as well as a long-duration negativity (LDN) in the last 400 ms of the 1400 ms epoch. N4 was earlier in latency, larger in amplitude, and larger over left hemisphere sites in response to monkey faces compared to human faces. It was also sensitive to the preceding or priming stimulus, exhibiting larger amplitudes when S1 and S2 matched than when they did not. Juvenile monkey ERPs showed N4-like peaks only at some sites. Nonetheless, they resembled adult N4s in their greater sensitivity to monkey faces and in their prominence over left hemisphere. Trained monkey waveforms exhibited an N2-P3 complex with P3 larger in amplitude and area, delayed in latency, and slightly larger over right hemisphere in response to monkey faces. Thus, N4 appears to be sensitive to conspecific faces and to the preceding stimulus, and is dominant over left hemisphere. Active processing results in P3-like components that may reflect the novelty and/or meaningfulness of the stimulus. The differences in hemisphere dominance between P3 and N4 suggest that they do not share the same neural sources.

#### The effects of locally administered adrenergic agents on monkey P300s.

Systemically administered adrenergic agents can have effects at a variety of peripheral and central sites. To control for these nonspecific effects, we are currently delivering small doses of L657,743 into specific cortical sites while subjects are exposed to the auditory/visual paradigms described previously. Preliminary results show that the bilateral P3 commonly recorded in these paradigms can be unilaterally affected with drug injections into the parietal cortex of one hemisphere.

#### The relationship between single unit and P300 activity in parietal cortex.

The role of the parietal cortex appears crucial for P300 electrogenesis. We are currently correlating activity of cells in areas of the parietal cortex with cortical P300 responses to auditory "oddball" events.

#### Similarities and differences between human and monkey face processing.

To develop a specific database of human ERPs for comparison with monkey responses to faces, we are currently recording human subjects in paradigms similar to those used with the non-human primates. Thus, the upright and inverted faces paradigm described previously is underway. Additionally, we have begun a study to address the configural/featural distinction in face processing. This will address the issue of hemispheric dominance for configural processing and left hemisphere dominance for featural processing.

#### The role of attention in cognition.

We are continuing studies in which monkeys are trained to respond to target stimuli in the right or the left hemifield and to ignore similar stimuli in the unattended field. Switching of attention is cued by the presence of a large box inside which the stimuli occur. To minimize eye movement artifact, subjects are being trained to fixate a small light in the middle of the screen.

**AIM 2: TO CORRELATE THE ACTIVITIES OF INDIVIDUAL MONKEY LC-NA NEURONS WITH CORTICAL NEURONAL ACTIVITY, ERPs, EEG CHARACTERISTICS, AND ASSOCIATED BEHAVIORS IN OPERANT PARADIGMS THAT UTILIZE VISUAL OR AUDITORY CUES.**

Locus coeruleus neuronal activity in awake monkeys: relationship to spontaneous EEG and auditory P300-like potentials. [Publication 7] These experiments were designed to test the hypothesis that novel auditory stimuli lead to phasic and/or tonic increases in locus coeruleus (LC) cell firing, which may be a necessary condition for the occurrence of P300 potentials. ERPs and LC unit activity were simultaneously recorded from 3 untrained macaque (Macaca fascicularis) monkeys during presentation of an auditory oddball paradigm. Oddball stimuli resulted in probability-sensitive, P300-like potentials. Three of 12 LC units showed small phasic enhancements of LC firing after infrequent but not frequent tones. A comparison between histograms elicited by the two types of stimuli revealed significant effects of stimulus sequence. One trained monkey displayed a prominent P300-like wave, but only when he performed the oddball task accurately. In sessions where the monkey did not respond, neither P300-like potentials nor phasic LC responses were elicited by target stimuli. LC cells tended to show a tonic elevation in firing following targets. In 2 LC cells recorded while the monkey performed the task, a phasic activation to targets was apparently related to behavioral response rather than stimulus presentation. These suggest that changes in LC activity during oddball paradigms might be very subtle, heterogeneous, and influenced by the subject's level of arousal and vigilance.

**AIM 3: TO REPRODUCE AND EXTEND OUR PRELIMINARY OBSERVATION THAT ACTIVATION OF THE LC BY LOCAL DRUG INFUSION, IN HALOTHANE-ANESTHETIZED RATS, PRODUCES EEG SIGNS OF CORTICAL AND HIPPOCAMPAL ACTIVATION.**

Effects of LC activation on neuronal activity in somatosensory cortex [Publication 8] As reported last year, in these studies a recording/infusion probe was used to activate the neurons of the LC in a reversible and verifiable manner in halothane-anesthetized rats. Infusions of bethanechol increased LC discharge rates 3- to 4-fold for a period of 3-5 min. Simultaneously, recordings were obtained from neurons in the hindlimb region of primary somatosensory cortex. These were activated by appropriate peripheral somatosensory stimuli (air puff or electrical stimulation delivered to the receptive field). Somatosensory responses and background activity were recorded during baseline conditions, LC activation, and LC recovery. Typically, several repetitions of this procedure were conducted for each cortical recording site, and only one recording site was tested per animal. The effects of LC stimulation were highly replicable both within and between animals. Baseline somatosensory responses consisted of a brief, short-latency activation followed by a longer duration pause, in which activity decreased to below background levels, and a gradual return to prestimulus discharge rates. During LC activation, the brief initial response was somewhat reduced, but the previous long-latency reduction in activity became an extended activation. Overall, the absolute magnitude of the total response was increased. Since background activity was reduced during LC activation, the ratio of stimulus-elicited to background activity was considerably enhanced. Thus, the effect of LC stimulation was similar in many regards to that previously reported for iontophoretic application of NE to cortical sensory neurons, although certain differences were also evident. In the last year, the analyses of these data have been completed and a manuscript describing these results submitted for publication.

Effects of LC inactivation on forebrain electroencephalographic (EEG) activity. [Publication 6] We have already published our studies demonstrating that LC activation induces cortical EEG desynchronization and hippocampal theta

activity. This year, we extended these studies by examining the effects of LC inactivation on EEG measures in halothane-anesthetized rats. Our recording/infusion probe was used to place 35-150 nl infusions of the  $\alpha_2$ -noradrenergic agonist, clonidine which inhibits LC neuronal discharge activity, immediately adjacent to the LC. The recording electrode allowed verification and quantification of the electrophysiological effects of these infusions. Simultaneously, EEG activity was recorded from sites in frontal neocortex (ECoG) and dorsal hippocampus (HEEG) and subjected to power spectrum analyses. Neither ECoG nor HEEG activity were substantially affected following unilateral clonidine-induced LC inactivation. In contrast, bilateral clonidine infusions that completely suppressed LC neuronal discharge activity in both hemispheres altered ECoG and HEEG status. The ECoG response to bilateral LC inhibition was characterized by a shift from low-amplitude, high-frequency activity to large-amplitude, slow-wave activity. Additionally, theta-dominated activity in the HEEG was replaced with mixed frequency activity. The onset of these changes in forebrain EEG activity was coincident with the complete bilateral inhibition of LC neuronal discharge activity, and they persisted throughout the period during which bilateral LC neuronal discharge activity was completely absent (60-240 min). The resumption of pre-infusion EEG activity patterns closely followed the recovery of LC neuronal activity or could be induced with systemic administration of the  $\alpha_2$ -noradrenergic antagonist, idazoxan.

Clonidine infusions (1 ng/nl) placed 800-1200  $\mu$ m from the LC were less effective at inducing a complete suppression of LC activity. These infusions either did not completely inhibit LC discharge activity (35 nl infusions), or did so with a longer latency to complete LC inhibition and a shorter duration of inhibition (150 nl infusions). In all of these cases, changes in forebrain EEG activity were not observed in the absence of the complete bilateral suppression of LC neuronal discharge activity. As with peri-LC infusions, the onset of ECoG/HEEG responses consistently coincided with the onset of complete bilateral LC inhibition, and EEG recovery was coincident with the reappearance of LC discharge activity.

These results suggest that the clonidine-induced changes in ECoG/HEEG were dependent on the complete bilateral suppression of LC discharge activity. Further, they indicate that under the present experimental conditions the LC/noradrenergic system exerts a potent and tonic activating influence on forebrain EEG state, such that elimination of LC neuronal discharge activity substantially increases synchronous activity in neocortex and decreases theta activity in hippocampus. These results are consistent with the proposed role of the LC/noradrenergic system in modulation of arousal state and state-dependent processes.

**AIM 4: TO EXAMINE THE RELATIONSHIP BETWEEN THE INTENSITY OF LC NEURONAL ACTIVITY AND RATES OF NOREPINEPHRINE (NE) RELEASE IN NEOCORTEX AND HIPPOCAMPUS BY PERFORMING MICRODIALYSIS IN THESE FOREBRAIN TERMINAL REGIONS IN ANESTHETIZED RATS DURING MANIPULATION OF LC ACTIVITY.**

Studies in anesthetized rat. These studies have been initiated (in collaboration with Dr. Ron Kuczenski) and substantial pilot data have been obtained as described in last year's report. However, we continue to have problems with our HPLC analyses and are exploring ways they can be improved.

Studies in unanesthetized monkey. This year we have successfully obtained microdialysis data from an awake monkey. A procedure for implanting reference

markers in the skull for use in MRI scans has been developed. A plastic stereotaxic apparatus was manufactured for use in these scans. The necessary hardware for holding a protective cap to prevent access of the animal to the probes and for holding the head during probe insertion were designed and machined. We performed an MRI on a monkey that was subsequently implanted with guide cannulae for dialysis probes. The cannulae were placed bilaterally over: 1) motor cortex (n=4); 2) parietal cortex (n=4); and caudate (n=4) at coordinates determined by the MRI. This monkey was habituated to the chairing procedure, including having the head fixed in position for 2-3 hours at a time. Following a 1-month recovery period, collection of dialysis samples was initiated. 2-3 dialysis probes were inserted per session, which consisted of 4 consecutive days. On day 1, the animal was chaired, the head fixed, dialysis probes inserted, the cap replaced and the animal returned to its home cage. On day 2, the animal was chaired, the head fixed, probes were connected to the perfusion pump, and sample collection was initiated. After 4 20-minute samples, amphetamine (0.25 mg/kg) was administered subcutaneously, and 3 additional samples were collected before the animal was returned to his cage. Days 3 and 4 were identical to day 2. At the end of day 4, the probes were removed and the probe recovery calculated. Sessions were separated by a 1-2 week period. Currently, almost all the sites have had one dialysis probe inserted. In subsequent sessions, we tested the feasibility of using a site a second time (a second session of 3 days).

The results up to this point have been very encouraging. Dopamine, norepinephrine, HVA, DOPAC and 5-HIAA were measurable in dialysate samples from both cortical regions and caudate. The probes remain useable over the 3-day session, and could likely be used for longer periods. Dopamine was present in baseline samples in the range of 100 fmol/sample for caudate, 2-7 fmol/sample for motor cortex and not detectable in parietal cortex. Amphetamine induced an approximately 10-fold increase in DA concentrations in caudate and motor cortex. At the time the motor cortex samples were being collected, the NE assay was not working. In parietal cortex, NE was present in baseline samples at a concentration of 2-4 fmol/sample. Amphetamine increased the concentration approximately 10-fold. As expected, NE was not detectable in baseline or amphetamine samples from the caudate. Consistent with current views regarding dopamine metabolism in primates, HVA was present in much higher concentrations than DOPAC in all regions, a pattern opposite that observed in rodents.

There are still adjustments that need to be made concerning dialysis cannulae design, probe design and cannulae implantation. However, these are minor changes and can most likely be worked out over the next 1-2 animals. A second monkey has undergone the MRI procedures and is scheduled for cannulae implantation in September, 1992.

An additional monkey has been implanted for use with a combined recording/infusion probe for recording from LC and making small infusions that will alter LC neuronal discharge rates. This monkey is trained in a motor task, and has undergone a few recording sessions. When the LC is located, the effects of LC activation/inactivation on behavior will be observed. If these studies demonstrate the feasibility of this approach, this technique will be combined with dialysis to study the relationship between LC activity, NE release, and behavior in awake, behaving monkeys. A well implanted over motor cortex will allow sampling from this cortical region in this monkey. Future monkeys will be implanted with dialysis probe guide cannulae.

## PUBLICATIONS

1. Foote, S.L., Berridge, C.W., Adams, L.M. and Pineda, J.A. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. *Prog. Brain Res.* 88:521-532, 1991.
2. Pineda, J.A. and Swick, D. Visual P3-like potentials in squirrel monkey: effects of a noradrenergic agonist. *Brain Res. Bull.* 28: 485-491, 1992.
3. Swick, D., Pineda, J.A., and Foote, S.L. Effects of systemic clonidine on auditory event-related potentials in monkeys. Submitted.
4. Pineda, J.A., Swick, D., and Foote, S.L. Noradrenergic and cholinergic influences on the genesis of P3-like potentials. In: Event Related Potentials of the Brain (Suppl. 42 to Electroencephalography and Clinical Neurophysiology). Ed: C.H.M. Brunia. pp. 165-172, 1991.
5. Pineda, J. A. and Nava, C. Event-related potentials in macaque monkey during passive and active processing of faces. *Beh. Brain Res.*, in press.
6. Berridge, C.W., Page, M.E., Valentino, R.J., and Foote, S.L. Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. Submitted.
7. Swick, D., Pineda, J.A., Schacher, S., and Foote, S.L. Locus coeruleus neuronal activity in awake monkeys: relationship to spontaneous EEG and auditory P300-like potentials. Submitted.
8. Adams, L.M. and Foote, S.L. Effects of locus coeruleus activation on spontaneous and sensory-evoked activity of neocortical somatosensory neurons. Submitted.